WHO/CDS/CSR/DRS/99.2

Containing Antimicrobial Resistance: Review of the Literature and Report of a WHO Workshop on the Development of a Global Strategy for the Containment of Antimicrobial Resistance

Geneva, Switzerland, 4-5 February 1999

World Health Organization
Communicable Disease Surveillance and Response

WHO acknowledges USAID's support of this Workshop

Contents

Page

A. Introduction

1. The Challenge

Since their introduction, antimicrobials (antibiotics) have played an essential role in decreasing morbidity and mortality due to infectious diseases. However, infectious diseases remain the leading cause of death worldwide. In recent years, infections caused by resistant strains of microorganisms have been increasing worldwide. The alarm bells are sounding. Concern has been echoed by the world's health community, with the adoption of a resolution on antimicrobial resistance at the World Health Assembly in 1998.

2. Antimicrobial use and resistance

Antimicrobials are used for treatment of infections and for prophylaxis against infections in humans and animals, for growth promotion in food animal rearing, and in agriculture. The widespread use of these compounds is thought to further encourage the emergence of antimicrobial resistance. However, although it is generally accepted that antimicrobial use promotes the emergence and spread of resistance, this acceptance is based primarily on indirect evidence and there are many aspects of the complex interactions between microbes, humans and antimicrobials that are as yet poorly understood. Nevertheless, it is generally believed that if selective pressures related to the excessive use of antimicrobials are eliminated and the opportunities for transmission of resistant organisms from person to person are reduced, the number of drug-resistant infections will decrease.

3. Development of a strategy for the containment of antimicrobial resistance

Since the emergence of resistance is a natural biological response of microorganisms confronted with the selective pressures imposed by the widespread use of antimicrobial agents, complete eradication of resistance is not feasible and the strategic aim must be one of containment, i.e. creating a situation in which both the emergence and spread of resistant micro-organisms are reduced and yet efficacious use of antimicrobials is maximized.

In developing such a strategy it is important to recognize the diversity of the microbes and the complex interactions between the microbial and human biological systems in the presence of antimicrobial agents. Numerous factors have been identified that affect antimicrobial use and any strategy designed to improve the use of antimicrobial agents must take all of these factors into account.

Although some interventions are reported to be efficacious in improving antimicrobial use and reducing the emergence and spread of resistance, there are considerable gaps in knowledge and further interventions need to be formulated and

tested. In addition, the impact of antimicrobial resistance on morbidity, mortality and the costs of treatment need to be further defined.

Since antimicrobial resistance is a global problem, the strategy should be relevant to both developing and developed countries. It is anticipated that governments will be able to use this global strategy as a basis for developing national strategies and that these will reflect different degrees of emphasis on different factors depending on the national situation.

4. The aim of this Workshop Report

The aim of this report is to provide a summary of the discussions and considerations brought forth at an international workshop held at WHO on 4-5 February 1999. The document is arranged in sections, including the literature review provided at the meeting which outlines those factors considered to be of major importance in the misuse of antimicrobial agents and the emergence and spread of antimicrobial resistance (Section B); a listing of those interventions considered by the meeting participants to be of greatest importance in controlling antimicrobial resistance (Section C); and finally, a list of knowledge gaps and research needs (Section D). A complete reference list and a list of the workshop participants can be found in Annexes 1 and 2 respectively.

How this document fits into the process of the strategy development

The workshop held in February 1999 constituted the first phase in the development of the global strategy for the containment of antimicrobial resistance.

This report provides a basis for further expert review and commentary to be used in the next phase of strategy development. Concurrently, a series of technical reviews has been commissioned on specific topics and these will provide additional reference material to strengthen the evidence-base for the global strategy. In collaboration with other partners, WHO is preparing the global strategy document which will be widely circulated for comment prior to a consensus meeting for final consideration.

B. Review of the literature as a basis for strategy development

1. Prescribers and dispensers

1.1. Factors contributing to misuse and/or resistance

1.1.1. Lack of knowledge

As stated in the Rockefeller University Workshop report, the issue of antimicrobial resistance receives limited coverage in medical school curricula (Tomasz 1994). This may result in less informed physicians who lack a defined understanding of antimicrobial resistance. This lack of knowledge is assumed to play a role in irrational prescribing (Kunin 1987). In many countries, the dispensers of drugs also may not be formally trained as dispensers or as pharmacists. In a study of 40 randomly selected health facilities in Ghana, only 8.3% of the dispensers had received formal training and there were no trained pharmacists at any of the facilities. (Ameyaw 1997) This factor can be extremely important as antimicrobials and other drugs are frequently purchased without visiting a physician. Bruneton *et al*. (1997) found that drug sellers in 7 countries in sub-Saharan Africa often advised non-essential drugs without adequate explanations and rarely suggested consultation of a physician.

1.1.2. Inadequate diagnosis

In areas where diagnostic facilities are not readily available (or are entirely absent), thus making differential diagnosis, organism identification, and knowledge of antimicrobial susceptibility patterns difficult, greater amounts of antimicrobials are often prescribed to 'cover any possible infection' (Bosu 1997). As resistance continues to become more prevalent, prescribers may be more likely to utilize broader spectrum antimicrobials for empiric therapy and prophylaxis of infections (Yu 1991; Goldmann 1997).

In a study of 'bare-foot' doctors in a district of Bangladesh, it was found that in areas without diagnostic services, antimicrobials were prescribed in 60% of all patients seen (Mamun 1991). This overuse of antimicrobials is further supported by Hogerzeil *et al.* (1993). In a study in 12 developing countries, 25% to 63% of all medications prescribed were antimicrobials (Hogerzeil 1993).

1.1.3. Incorrect drug selection for treatment or prophylaxis of infections

In a study conducted in China, 63% of the antimicrobials selected to treat proven bacterial infections were deemed inappropriate (Hui 1997). In another study in Bangladesh, it was determined that 50% of all the prescriptions for antimicrobials in a hospital unit were considered inappropriate (Hossain 1982).

1.1.4. Dose/duration/route incorrectly prescribed

In a retrospective study from Vietnam looking at antimicrobial dosages, it was found that more than 70% of patients were prescribed inadequate dosages of antimicrobials (Chalker 1997). Gumodoka *et al.* (1996) reported that although one out of every four patients in their medical districts received antimicrobials by injection, approximately 70% of the injections were avoidable. The majority of these treatments were for respiratory, skin and urinary tract infections.

Long treatment duration and sub-therapeutic or sub-optimal dosages have been correlated with increases in selective resistance (Rice 1990; Guillermot 1998).

1.1.5. Prescriptions in response to patient pressures

Patient demand for antimicrobials has been shown to increase unnecessary antimicrobial prescriptions (Bauchner 1997; Bosu 1997; Macfarlane 1997). In a study by Macfarlane *et al*. (1997), patient pressure was the most common influence in the decision to prescribe antimicrobials even when the physician thought they were not indicated. This type of prescribing can lead to a 'perpetual' cycle if patients repeatedly receive antimicrobials even if they are not indicated, which then enhances their belief that antimicrobials are necessary and they continue to request them (Little 1997; Macfarlane 1997)[see also Section 2, patients: the public]. Patient pressure as to the route of administration of antimicrobials has been reported as some patients believe that injections are more efficacious and work faster in treating infections. Health care workers report that patient demand for injections has led to an over-prescribing of injectable antimicrobials (Gumodoka 1996).

1.1.6. Fear of litigation

Fear of litigation has been suggested as one reason physicians over-prescribe antimicrobials (Fidler, 1998).

1.1.7. Financial gain

In countries where physicians are underpaid, pharmaceutical companies have been known to pay prescribers a commission for prescribing their products (Norrby 1996). In addition, pharmacists and dispensers gain financially from over-dispensing and through dispensing more expensive broad-spectrum agents when cheaper narrow spectrum agents would suffice.

1.1.8. Response to promotional pressure

It is recognized that often the main resources of drug information for prescribers are drug representatives and commercially oriented publications. This was confirmed in a study by Bosu (1997). [Also Section 5]

1.2. Interventions related to prescribing and dispensing factors

1.2.1. Understanding drug use patterns

A first step to improving rational use of antimicrobials is to understand prescribing patterns. This will aid in the identification of areas for potential interventions to improve use (Bosu 1997). Using indicators and methods described in the WHO manual "How to investigate drug use in health facilities" (WHO 1993), it is possible to describe drug use patterns and prescribing behaviour. After undertaking interventions to improve drug use, these same indicators can further be used to measure impact

1.2.2. Education on appropriate use

A combination of national prescribing guidelines and educational campaigns on appropriate use of antimicrobials targeted at prescribers has had some success in reducing specific patterns of antimicrobial resistance (Seppala, 1997). In addition there has also been some success in the use of educational campaigns targeted at prescribers and patients to recognize that not all infections require the use of antimicrobials. Included in this same campaign was a message to parents to discourage them from sending their sick children to day-care to reduce opportunities for transmission of infection (Kristinsson 1995).

In an effort to reduce 'reconsultation' of patients, Macfarlane and colleagues (1997) utilized a patient information leaflet regarding coughs. In patients not prescribed antimicrobials, a trend was observed, although not statistically significant, between those given the educational leaflet and the incidence of not reconsulting. The use of delayed prescribing techniques has been proposed when physicians feel 'pressured' into prescribing antimicrobials (Cockburn 1987; Butler 1998). Some physicians say that they promise a free return visit if the patient feels that a reconsultation is necessary because they did not receive antimicrobials (Butler 1998).

Because inappropriate prescribing is rarely due to a lack of knowledge alone, many studies have found that the use of only printed material without other forms of supporting interventions are ineffective in altering prescribing behaviours. (Soumerai 1989; Mabadeje 1997)

The use of academic detailing or 'unadvertisements' and educational programmes directed to physicians have been shown to decrease antimicrobial usage/misuage (Avorn 1983; Harvey 1986; Molstad 1994; Gani 1997). Unfortunately none of these studies looked at resistance as an outcome or impact indicator.

It has been suggested that increasing the problem-based pharmacotherapy training for medical and paramedical students can have a positive impact on long term good prescribing habits. The use of the WHO "Guide to Good Prescribing" (De Vries *et al.* 1994), a manual designed to support problem-based learning for medical students, has demonstrated a positive impact on prescribing skills of 219 students in

seven medical schools (De Vries *et al.* 1995). [Also see Section 5, private industry, for additional educational interventions for medical students]

Improving the drug education of non-physician prescribers and dispensers is also a recommended step in improving drug use. In a study in Ghana, educational interventions aimed at dispensers significantly improved drug use by increasing the percentage of appropriate labelling and patient knowledge of their medications (Ameyaw 1997). In the Philippines as well, interventions targeted at local drug sellers significantly improved their quality of practice (Sia 1997).

1.2.3. Policies to reduce antimicrobial use

Coast *et al.* (1998) explored economic perspectives of policies used to decrease antimicrobial resistance. They discuss several techniques such as regulation (controlling prescribing via policy/guidelines or by enforcing a global limit to prescribing of antimicrobials), permits (allowing physicians to prescribe up to a certain quantity of antimicrobials per permit) and charges (levy taxes on antimicrobials). In their model, they suggest that the use of permits may offer an economic method of reducing antimicrobial resistance. [See also Section 4].

1.2.4. Maximizing appropriate antimicrobial prescribing

There has been much discussion regarding the appropriate selection, best dosage, or best dosing interval of antimicrobials in the attempt to avoid the selection of resistance as well as which parameters to use to verify various hypotheses (Drusano 1998; Schentag 1998; Thomas 1998). In addition, the use of antimicrobials in combinations has been suggested for some infections, as a trend has been observed of a reduced incidence of resistance when combination therapy has been employed (Milatovic 1987; Hilf 1989).

In general, clinical drug trials have not been designed to determine the most appropriate duration of antimicrobial therapy, and thus the duration of therapy is generally prescribed following package insert recommendations. Many scientists and clinicians believe that shorter treatment courses for many infections are likely to be as equally effective as the longer courses (Pichichero 1997). A potential benefit of shorter course therapies may be to decrease the selective resistance pressures of antimicrobials on microorganisms. It addition, shorter lengths of therapy are more readily adhered to by patients.

The careful selection of antimicrobials is an important factor in the development of resistance as it appears that some antimicrobial agents may be more likely to select or promote resistance (Loulergue 1994; UK Department of Health 1998). [See also Section 7].

2. Patients: The Public

2.1. Factors contributing to misuse and/or resistance

2.1.1. Self medication

Self medication is often cited as a major contributing factor to drug resistance (Vuckovic 1997). In a Brazilian study, it was determined that the three most common types of medication used by villagers were antimicrobials, analgesics and vitamins with the majority being prescribed by a pharmacy attendant or purchased by the patient without prescription (Haak 1988). This is important as many antimicrobials are often inadequately dosed or do not contain adequate amounts of active drug (Kunin 1987).

2.1.2. Poor adherence

In a literature search conducted in 1988, over 4000 English articles were available in the literature on patient adherence/compliance with more than 75% of them having been published within the previous 10 years (Trostle 1988). In a majority of the studies, it was reported that a lack of patient understanding and provider communication led to most instances of non-adherence (Sackett 1979; Buckalew 1986). This factor is critical as often patients who fail to complete therapy (such as in the case of tuberculosis) will relapse and require retreatment. Previous treatment is considered an important factor in the selection of resistant bacteria (Bloom 1992).

2.1.3. High need (poor underlying health)

Malnutrition and poor underlying health can contribute, through increasing susceptibility to infection, to greater usage of antimicrobials.

2.1.4. Misinformation/inappropriate beliefs; patient over-reliance on antimicrobials

In a survey of 3610 patients conducted by Braithwaite and colleagues (1996), over 50% of interviewees believed that antimicrobials should be prescribed for all respiratory tract infections with the exception of the common cold. It was also reported that 81% of patients expected to see a definite improvement of their respiratory symptoms after 3 days, and 87% reported that feeling better is a suitable reason for cessation of antimicrobial therapy. In addition, most of these patients believed that remaining antimicrobials could be saved and used again at a later time.

In the Philippines it is reported that people believe that isoniazid is a ‘vitamin for the lungs’ and many mothers purchase isoniazid syrup for children with ‘weak lungs’ in the absence of documented tuberculosis (Querubin 1986). In another study, patient demand caused one pharmacy in South India to stock over 25 (of the over 100 available) brands of co-trimoxazole. Patients familiar with the brand name of Septrin led physicians to prescribe the same drug under different names (Nichter 1994).

2.1.5. Poverty-associated undertreatment

A lack of access to drugs due to economic hardship has been described as a factor for impacting resistance as appropriate therapy can be interrupted. In many developing countries, for economic reasons antimicrobials are purchased in single doses and may be only taken for a couple of days until the patient 'feels better'. This action has the potential for impacting the emergence of resistance (Couper 1997; UK Department of Health 1998).

2.1.6. The 'Expensive is better' myth

It has been suggested that many patients believe that more expensive medications are more efficacious (a belief also shared by some prescribers and dispensers). This results in the unnecessary use of newer, more costly, broader spectrum antimicrobials and encourages the selection of resistance to these agents. It also results in unnecessary expenditures.

2.1.7. Expectation of treatment

Patients commonly expect to receive prescriptions upon a visit to their physician and it has been described that patients' expectations for a prescription are met approximately 75% of the time by the prescriber. As shown by Macfarlane *et al*. (1997), 85% of patients thought their respiratory symptoms were caused by infection, 87% believed that antimicrobials would help and one fifth of these patients specifically asked their physician to prescribe an antimicrobial (Macfarlane 1997).

2.1.8. Response to advertising

Direct-to-consumer advertising allows pharmaceutical manufacturers to market prescription drugs directly to the public. Generally, multi-media such as television, radio and print are utilized. The goal of direct-to-consumer advertising is to induce consumers to purchase products that they may not otherwise purchase. This factor is further complicated by the fact that the targeted audience (the public) is rarely the one who prescribes or pays for the medication(s).

Direct-to-consumer advertising has been noted to have "the potential to stimulate demand by playing on the consumer's relative lack of sophistication about the evidence of that supports the use of one treatment over another" (Shapiro 1997). These advertising methods are quite effective as described in a paper by Vuckovic and Nichter (1997), where pharmacists reported being able to guess the topics of the previous day's television shows based upon the daily customer requests for medications.

In a telephone survey of consumers regarding direct advertising, 66% believed that advertisements for prescriptions would provide useful information and 88% said that they would seek out more information about a drug that they saw advertised on

television or in print. On the other hand, 63% disagreed with the statement that most people would be able to tell if they were being misled by the advertisements (Morris 1986).

An American study demonstrated that most physicians surveyed (95%) had encountered an average of 7 patients within the previous 6 months who had specifically requested drugs as a result of direct-to-consumer advertising (Lipsky 1997). Over 70% of the physicians reported that patient requests as a result of direct-to-consumer advertisements had lead them to prescribe a pharmaceutical agent that they might not have otherwise chosen.

Recently the United States Food and Drug Administration (FDA) has proposed new guidelines that lift previous restrictions on direct-to-consumer advertising and allow the pharmaceutical manufacturers greater freedom on advertised health claims. A two-year evaluation period has been proposed to assess the impacts and implications of the new guidelines ('T Hoen 1998).

[Also see Section 5, private industry]

2.2. Interventions related to patient factors

2.2.1. Improving adherence

Many methods have been used to ensure adherence to antimicrobial therapy. These include the use of fixed dose combinations (to minimize the number of tablets or capsules to be taken), special calendars, blister packing, directly observed therapy (DOTS) for tuberculosis (Frieden 1995) and more simplified therapy (Cockburn, 1987). DOTS has been shown to significantly decrease acquired resistance in tuberculosis (Weis 1994) and this strategy is currently being studied globally (personal comment, M. Espinal, WHO).

2.2.2. Patient/public education

Education of patients about the name, dosage, description and common adverse effects of their medication(s) has been used to increase adherence (Sharpe 1974). A greater interaction between health providers and consumers for health and drug (antimicrobial) related education has been proposed. As T Hoen (1998) states "Health professionals, including pharmacists, have a responsibility to build partnerships with consumers and patients. This partnership and cooperation is essential in the political arena in which health care policies are set so that sensible arguments can be made against strong commercial pressures…".

The WHO Action Programme on Essential Drugs (DAP) convened a consultation to address the need for public education in rational drug use (WHO 1994) and since has produced a document "Rational Drug Use: Consumer Education and Information" (WHO 1996). This document discusses the practical issues and dilemmas related to the need for rational drug use education, its priority and content, underlying principles and target population. In a study carried out in Peru, a

multifaceted educational intervention directed at the community using media, face-to-face meetings and training on the use of medicines was successful in decreasing the inappropriate use of antidiarrhoeals and antimicrobials for simple diarrhoea (Paredes 1997).

3. Governments and health systems

3.1. Factors contributing to misuse and/or resistance

3.1.1. National policies poorly communicated, not implemented, or poorly implemented with little or no adherence

A lack of support in actively marketing the Essential Drugs List (EDL) in Ghana has shown that it has had little impact on prescribing (National Drugs Committee 1994) nor is it even available in many government health facilities (Bosu 1997). In a study in two villages in Brazil, around 50% of all medications used were not found on the country's EDL or on the WHO Model List (Haak 1988).

3.1.2. Regulatory mechanisms ineffective and/or substandard drugs/lack of quality assurance

The Counterfeit Intelligence Bureau estimated that in 1991, 5% of the world's trade was counterfeit. This percentage is likely to be higher for pharmaceuticals that are easily transportable and are in great demand (WHO 1992). Such counterfeit products have bypassed regulatory controls for quality assurance, thus potentially resulting in medications that contain too little or none, or even entirely different active ingredients.

3.1.3. Sales not regulated, informal sector sales

Although antimicrobials are prescription-only medicines in many countries, there is a wide variation between the law and what is actually practised. In Spain for example, antibacterial agents can be purchased in most pharmacies despite having prescription-only status (UK Department of Health 1998) and in many developing countries antimicrobials can be purchased without prescription (Levy 1987; Hui 1997; Hart 1998). In a study of chemist shops in Nairobi, it was discovered that 64% of chemists sold antimicrobials without physicians' prescriptions. In addition, most would sell incomplete treatment courses at the request of the patient (Indalo 1997). In a study of a rural village in Bangladesh, 95% of all medications consumed were obtained from pharmacies with only 8% having been prescribed by graduate physicians (one-third of these medications were anti-infectives) (Hossain 1982).

3.2. Interventions related to government and health systems factors

3.2.1. Establishing essential drugs lists and essential drug policies

In 1977 the first WHO Model List of Essential Drugs was developed with the goals of promoting access to and the rational use of drugs. This document contains a selected number of antimicrobials, has been revised regularly and serves as a guide for countries in determining their national drug policies. At present over 120 countries have implemented an EDL.

In a study comparing areas where Essential Drug Policies (EDPs) were and were not functioning, those areas in which an EDP existed had more essential drugs available, with stocks to last three times longer than in the areas without programmes. In addition, significantly fewer injections and antimicrobials were utilized in areas with a national EDP. It was concluded that programmes significantly improved the availability and rational use of essential drugs (Hogerzeil 1989). A retrospective study of prescribing practices in Ethiopia found a significant decrease in the prescribing of non-essential drugs after introduction of an EDL (Lindtjorn 1987). It has been suggested that an EDL is most effective when supported by educational programmes and follow-up (Hogerzeil 1995).

3.2.2. Establishing National Standard Treatment Guidelines

It has been suggested that National Standard Treatment Guidelines be developed in connection with the countries EDL. These national guidelines can then be further adapted for local hospital specific use. As is true with the EDL, national guidelines are more effective in combination with supporting interventions such as training and supervision (Kafuko 1997). Such guidelines must be regularly updated and reviewed as well.

[See Section on 4, hospitals, for more information on treatment guidelines]

4. Hospitals

4.1. Factors contributing to misuse and/or resistance

4.1.1. Lack of hospital therapeutics committee

While no references were found relating this to misuse or resistance, it is considered a necessary component of an antimicrobial control programme.

4.1.2. Lack of antimicrobial policies, policies not updated with surveillance data and/or poor information flow

Hospitals serve as an important source for learning of prescribing practices for students. Unfortunately, this prescribing is often irrational. In an analysis of prescribing practices in 10 studies from teaching hospitals world-wide, overall 41-91% of all antimicrobials prescribed were considered inappropriate (Hogerzeil 1995).

[Also see Section 3, governments and health systems regarding EDL and STG]

4.1.3. Lack of infection control committees, procedures or guidelines

As the principles of hand-washing and/or changing of gloves before and after contact with patients are often disregarded (Albert 1981; Graham 1990; Larson 1995; Goldmann 1997), dissemination of resistant bacterial strains in hospital and health care facilities is increased. The spread of resistance is widening as patients move from intensive care wards to general wards and then to the community, or between hospitals and nursing homes (Riley 1984; Ayliffe 1997; UK Department of Health 1998).

4.1.4. Lack of sterile supplies

As it has already been documented, especially in light of HIV/AIDS, infections can be transmitted via non-sterile injection equipment. In a study of health facilities in Tanzania, it was also shown that 40% of the supposedly sterilized needles and syringes were bacterially contaminated (Gumodoka 1996).

4.2. Interventions related to hospital factors

4.2.1. Multi-faceted/interdisciplinary approach

Multi-disciplinary and integrated approaches to reduce antimicrobial use in hospitals have been proposed as a solution by many experts (Goldmann 1997; Hughes 1997; Acar 1998; Struelens 1998). Hospital administrators, clinicians, infectious diseases specialists, infection control teams, microbiologists and hospital pharmacists all have a role and their coordination is vital. The integrated responsibilities that can be undertaken include formulary-based guidelines, monitoring and evaluating drug use, surveillance and reporting of hospital resistance patterns, detection and appropriate care of patients with resistant commensal organisms, and promotion and monitoring of basic infection control practices (Struelens 1998).

Although there is little information regarding the impact of a hospital therapeutics committee (also called pharmacy and therapeutics committee) in developing countries, their beneficial role in the promotion and monitoring of drugs as well as cost containment has generally been established in developed countries (Soumerai 1984; Weekes 1996). Therefore, it is recommended that hospital therapeutics committees be established in developing country hospitals.

4.2.2. Use of formularies/control policies/treatment guidelines

The use of formularies has been suggested as a method for decreasing inappropriate prescribing and generally reducing expenditures. It has been suggested that a formulary should be ‘flexible’ and depend on cost-effectiveness and patterns of resistance (Levy 1987). If antimicrobial control programmes are to be effective, it is important to ensure consistent longterm monitoring. Although, decreases in resistance were observed with the use of control programmes as soon as monitoring was relaxed, resistance quickly increased (US Congress Report 1995).

In a review of clinical guidelines (Grimshaw 1993), it appeared that they can improve decision-making and as a result, improve patient care. It has been suggested that programmes utilising clinical guidelines that are supported by other interventions such as education, peer review, etc, are more effective than those without support (Goldmann 1996). In an observational study of one hospital with a computerized prescribing guideline system that encouraged appropriate use of antimicrobials, trend analysis showed that hospital resistance patterns stabilized over a seven-year period (Pestotnik 1996).

In a study by Recco *et al.* (1979), although prescriber education combined with hospital antimicrobial control policies led to decreased antimicrobial costs and improved prescribing, resistance was not reduced. In fact, resistance increased in many common gram-negative infections.

It has been suggested that hospital formularies may be a contributing factor in the selection of resistance by being very restrictive (Schentag 1995). In a survey in the USA, although a great majority of the hospitals had implemented formularies as a method for decreasing antimicrobial costs, most replied that expenditures had actually increased. The most commonly cited reason for this increase was the problem of drug resistance (Rifenburg 1996).

Clinical guidelines focussed on use of injectable antimicrobials necessary to treat infections and the proper sterility of needles and syringes, as well as health education programmes, were used to raise awareness about the effectiveness of oral medications and the possible adverse effects of injected medications. This resulted in greater knowledge of health care workers on the appropriate use of injectable antimicrobials, decreased contamination of syringes and needles and a reduction in patient demand for injections (Vos 1998).

Targeted antimicrobial control policies in combination with improved hygiene (often including education) have reduced antimicrobial resistance in some settings (Barber 1960; Giamarellou 1997).

Antimicrobial order forms have been used with success in improving antimicrobial prescribing in some hospitals (Avorn 1988; Gyssens, 1997) but other studies have documented that orders had no effect on improving antimicrobial prescribing (Aswapokee 1992).

The cycling of antimicrobials within a health care institution has been suggested as a possible intervention to decrease drug resistance. This technique alternates formulary antimicrobials between drug classes every several months and theoretically reduces the selective pressure of one antimicrobial class (Schentag 1998). However, this hypothesis is challenged by a study that showed that cycling can replace one resistance problem with another (Urban 1993).

Therapeutic selection of antimicrobial agents has been proposed as a method for decreasing resistance. A study by Betts and colleagues (1984) examined the impact

of changing the hospital formulary aminoglycoside (from gentamicin to amikacin) on development of resistance in various gram-negative bacteria. In the 5 years following the intervention, gram-negative resistance rates to gentamicin decreased with little development of amikacin resistance.

In a mathematical modelling study, Bonhoeffer *et al.* (1997) evaluated various types of interventions that have been widely discussed for reducing antimicrobial resistance in hospitals. They compared antimicrobial cycling, combination therapy and 50-50 therapy. 50-50 therapy is also known as 'switch back therapy', where one of two antimicrobials are alternately selected each time a new patient is treated. For example patient 1 receives antimicrobial A, patient 2-antimicrobial B, patient 3-antimicrobial A, patient 4-antimicrobial B and so forth). They determined that although 50-50 therapy was equal to or better than antimicrobial cycling, combination therapy was better than both of these other methods (except when the resistance genes of the two drugs are carried on the same plasmid).

4.2.3. Emphasis on better handwashing techniques

It has been suggested that interventions such as education and motivational programmes, improvement of equipment, performance feedback (among others) can increase adherence to improved handwashing (Larson 1995). The basic aspects of hygiene have been shown to be important in reducing infection transmission rates (and thereby the spread of resistance); Mayer *et al.* (1986) showed that improved handwashing and/or use of gloves and gowns did lead to decreased infection rates.

5. Private industry

5.1. Factors contributing to misuse and/or resistance

5.1.1. Industry/wholesaler/retailer pressure to sell and/or over-promotion/misleading promotion

In a number of sources, it is clearly described that advertising and promotion by the pharmaceutical industry is a major and powerful source of information for prescribers (Avorn 1982; Zarate 1995). In a review of the literature on the interactions between physicians and the pharmaceutical industry, it was concluded that there was strong evidence that these interactions influence prescribing behaviour (Lexchin 1993).

It has been suggested that physicians may not even be aware of these influences. In a study by Avorn *et al.* (1982), although most prescribers believed that drug advertisements and detail men played a role of 'minimal importance' in influencing prescribing patterns and academic sources of information were 'very important', it appeared that the opposite was actually true. This finding was further confirmed by a study of prescribing habits of physicians in Peru (Zarate 1995). Although over two-thirds of physicians surveyed claimed their primary source of drug information came from medical literature, the study concluded that advertising materials distributed by pharmaceutical companies appeared to be a key source of information for prescribers. The authors went on to say that this factor "tended to promote irrational drug use."

In a study by Wilkes *et al.* (1992) investigating the quality of advertisements in medical journals, experts were asked to evaluate the appropriateness of advertisements for publication in the form in which they actually appeared. They concluded that 28% of the advertisements should have been rejected and another 34% should have had major revision before publication.

5.2. Interventions related to private industry factors

5.2.1. National or local guidelines

Many countries have instituted guidelines and codes for pharmaceutical companies to deter them from misleading promotion. As reported by Lexchin (1997), not only do these codes vary between countries but they also vary as to the manner in which they are executed.

Education of medical students in the Philippines showed that the group of students who underwent a four hour course in evaluation of drug promotional materials scored significantly better than those students in the control group when questioned on 'violations of existing guidelines' on drug promotion (Alvero 1997).

6. Non-medical uses of antimicrobials

6.1. Factors contributing to misuse and/or resistance (impacting human health)

6.1.1. Growth promoters in food animals, treatment and disease prevention in food animals, agriculture and aquaculture

Most of the factors affecting emergence and spread of antimicrobial resistance and misuse of antimicrobials already described in previous sections also apply to the non-medical use of antimicrobials. For prescribers and dispensers, education is lacking on antimicrobial resistance and appropriate antimicrobial therapy. In many countries, therapeutic antimicrobials are dispensed by inadequately trained individuals. By far the largest amount of antimicrobials is applied to animal flocks and herds through feed with inherent problems of accurate dosing and inevitable treatment of all animals irrespective of health status. Empiric treatment predominates because of the widespread lack of diagnostic services (particularly in developing countries) and may often be, from the producers' viewpoint, economically contraindicated. Sales of drugs constitute 40% of the income of veterinarians in some countries (ACMSF report, 1999).

As noted in Section 3, inefficient regulatory mechanisms or poor enforcement of regulations, with lack of quality assurance and marketing of substandard drugs, are also important contributory factors. Discrepancies between regulatory requirements and prescribing/dispensing realities are often even wider than in human medicine. In some countries, even injectable antimicrobials for disease treatment in animals are sold over the counter (World Health Organization, 1997). Antimicrobial growth promoters are not considered as drugs and are licensed, if at all, as feed additives.

Marketing of antimicrobials and growth promoters by private industry influences prescribing behaviour and use patterns of veterinarians, feed producers and farmers.

Reports from North America and Europe estimate that about 50% (in tonnage) of all antimicrobial production is used in livestock production (including poultry) (FEDESA, 1998). Antimicrobials are used as growth promoters (in sub-therapeutic doses), prophylactically for disease prevention (e.g. after co-mingling of animals from different farms), and therapeutically, for treatment of infections in animals. The increasing production of food of animal origin under 'industrialized' conditions has contributed to the increased use of antimicrobials.

The consequences of selecting resistant bacteria in animals include:

- An increase in the prevalence of resistant bacteria in animals;

- The increased potential for transfer of resistant pathogens to humans by direct contact with animals or through the consumption of contaminated food or water. The transfer of resistance genes from the animal to the human bacterial flora;
- The potential for resistant infections and therapeutic failures in animals and humans. The increased prevalence of foodborne disease from pathogens of animal origin suggests that the risk of human acquisition of resistant zoonotic pathogens is increasing.

In addition, the impact of the widespread distribution of non-metabolized antimicrobials through sewage into the environment and other ecosystems is unknown.

6.1.2. Problems with specific pathogens or drug classes: salmonella, campylobacter, enterococci

There is direct evidence that antimicrobial use in animals selects for antimicrobial-resistant non-typhoid *Salmonella* serotypes (Glynn *et al.*, 1998; Holmberg *et al.*, 1987). These bacteria are transmitted to humans mainly through food or direct contact with animals. Resistance limits the therapeutic options available for the small subset of clinical cases of invasive non-typhoid *Salmonella* infections which require antimicrobial treatment. A recent example is a clone of *S. typhimurium* DT104, resistant to ampicillin, tetracycline, streptomycin, chloramphenicol and sulphonamides, which has become prevalent in many countries including the UK, Germany and the USA (Glynn *et al.*, 1998)).

Following the introduction of fluoroquinolones for use in food-producing animals, the emergence of *Salmonella* serotypes with reduced susceptibility to fluoroquinolones in humans has become a cause for particular concern. This phenomenon has been observed in countries such as France, Germany, Ireland, the Netherlands, the Russian Federation, Spain and the UK (WHO Report, 1997). There has been little documented impact of this resistance on human health to date, but there is concern about the potential human health consequences if resistance were to increase and spread. This has been substantiated by a recent outbreak of quinolone-resistant *S. typhimurium* DT104 resulting in treatment failures in hospitalized patients in Denmark (Moelbak *et al.*, 1999).

Following the introduction of fluoroquinolones for use in poultry, there has been a dramatic rise in the prevalence of fluoroquinolone-resistant *Campylobacter jejuni* isolated in live poultry, poultry meat and from infected humans. Moreover, prior to any use in poultry, no resistant strains were reported in individuals without previous exposure to quinolones (WHO Report, 1997). Because of their broad antibacterial spectrum, fluoroquinolones are often used in humans for empirical treatment pending laboratory results. The effect of fluoroquinolone resistance in *Campylobacter* on the clinical outcome of treatment with a fluoroquinolone is not clear.

The use of avoparcin as a growth-promoting feed additive in animal husbandry has contributed to the reservoir of transferable resistance genes to glycopeptides,

including vancomycin, in the commensal enterococci of animals. Glycopeptide-resistant enterococci from animals can reach humans via the food chain. Although glycopeptide resistance genes have been shown to be widely disseminated, the extent to which the gene pool in animals contributes to the prevalence of glycopeptide-resistant commensal enterococci in humans has not been quantified. Glycopeptide-resistant enterococci cause serious infections in hospitalized immune-impaired patients. In this setting, they contribute to increased morbidity and mortality, in part because of limited therapeutic options.

There is concern that there will be increased dissemination of glycopeptide resistance genes among *Enterococcus faecalis* and their spread to other gram-positive bacteria, particularly to multi-resistant *Staphylococcus aureus* for which vancomycin is the drug of last resort. Due to the limited number of agents available for the treatment of glycopeptide-resistant enterococcal infections in humans, antimicrobial agents not previously used in human medicine are being investigated, including drugs from classes currently used as growth promoters in animals. Therefore the selection of further resistance in enterococci in animals is undesirable, *e.g.*, streptogramin resistance due to use of virginiamycin as a feed additive in animals.

6.2. Interventions related to 'non-medical' factors

WHO has recommended that those antimicrobials that select for resistance to agents used for human treatment should not be used in animal husbandry. It was re-emphasized that antimicrobials should not be a substitute for healthy hygiene in animals and that excessive use of antimicrobials should be reduced (WHO 1997). However, in an editorial of March 1998, it was noted that no changes in antimicrobial use in animals in the USA have resulted from these recommendations (Levy 1998). In Europe in 1998, four major growth promoters (bacitracin, tylosin, spiramycin, virginiamycin) were banned. Limited studies from Germany and Denmark have shown that ban of avoparcin in animals in Europe has led to a reduction in the prevalence of vancomycin-resistant enterococci in poultry and in healthy individuals (Wegener 98, Klare *et al.* 97). Sweden banned the use of growth promoters in livestock and poultry in 1987 and subsequently there has been a marked reduction in antimicrobial consumption in animals. Prevalence of antimicrobial resistance in *Salmonella* isolated from animals in Sweden has fallen significantly since 1985.

Improvements in animal production hygiene have also been recommended to reduce the need for antimicrobials (WHO, 1997) and some studies (Wierup 1997)) have shown that such improved hygiene and reduced use can be achieved without loss in productivity.

7. Microbial determinants

7.1. Factors causing emergence and augmentation of resistance

Bacteria have evolved many different mechanisms of resistance. These can be classified as: a) alteration in, or addition of, the target site of antimicrobial binding; b) alteration in access to the target site (e.g. decreased permeability of cell wall; efflux mechanisms); and c) inactivation of the antimicrobial (e.g. beta-lactamases). Furthermore, resistance may arise through mutation or by acquisition of resistance genes (horizontal transmission) from another bacterial species.

Given that there are different classes of antimicrobials each with a different molecular target site and the fact that a single bacterial species may exhibit more than one of these mechanisms against a single class of antimicrobial (e.g. change in penicillin binding protein target site and production of beta-lactamase is a common feature of methicillin-resistant *Staphylococcus aureus),* the genetic basis and the phenotypic expression of resistance is extremely complex.

It appears that some bacterial species more readily develop (or acquire) resistance than others when exposed to apparently similar selective pressures. *Shigella* spp. and *Staphylococcus aureus* developed resistance rapidly as each new class of antimicrobial was introduced (with some exceptions, e.g. vancomycin resistance in *S. aureus*). In contrast, *Streptococcus pneumoniae* infections have been treated with penicillin for many years but only relatively recently has this species developed penicillin resistance. This may be because the mechanism of penicillin resistance in *S. pneumoniae* is complex and has taken a long time to evolve. Meanwhile, *S. pyogenes,* a human pathogen in the same genus that must have had exposure to penicillin similar to that of *S. pneumoniae,* remains completely susceptible to penicillin. However, erythromycin and tetracycline resistance are widespread, in *S. pyogenes*. Among opportunist hospital pathogens, *Enterobacter* spp., for example, have a great propensity for becoming resistant due to beta-lactamase production to expanded spectrum cephalosporins, leading to treatment failure (Chow 1991, Olsen 1983). *Pseudomonas aeruginosa* behaves similarly. Little is known about why these different bacterial species develop antimicrobial resistance at such different rates.

It is reported that some antimicrobial agents may be more likely to select or promote resistance (Loulergue 1994; UK Department of Health 1998) than others. Recently, concern has been expressed about the impact of long half-life antimicrobials on the development of selective bacterial resistance. Although these agents may improve compliance because they can be dosed less frequently, their long half-life may expose bacteria to prolonged periods of sub-therapeutic concentrations of a given agent and thus lead to the selection of resistance (Baquero 1997; UK Department of Health 1998). Despite widespread use for more than 40 years, resistance to nitrofurantoin among *E coli* being treated with this antimicrobial has not developed.

C. Interventions to contain antimicrobial resistance

The following items were identified by the workshop participants for consideration as potential components of a comprehensive programme for containment of antibiotic resistance. The components are not prioritized here nor are they ranked as to the quality of evidence supporting their effectiveness. Some recommendations were made by several groups and are thus relevant in several different discussion areas but to avoid redundance have been listed only under one category.

1. Prescribers and dispensers

1.1. Description of current antimicrobial use practices and identification of the determinates of those practices.

- Determine current antimicrobial use practices and the determinants of those practices within each institutional, local or national setting.

1.2. Behaviour change strategies and interventions.

- Prioritize for intervention those conditions and circumstances in which the majority of antimicrobial use and misuse occurs.

- Evaluate the impact of these programmes once implemented.

- Target specific programmes for each category of provider and dispenser, including trained providers (physicians, midlevel providers, physician assistants, nurses, medical aids); authorized dispensers (pharmacists); and unauthorized dispensers (drug sellers, traditional healers, others).

- Utilize elements of behaviour change theory to develop programmes to modify inappropriate antimicrobial prescribing and dispensing within each of these groups of providers.

1.3. Education and Clinical Practice Guidelines.

- Ensure enhanced education of providers regarding appropriate antimicrobial use by implementing specific training on this topic at all levels, including professional school, post graduate in-service education, and exposure to opinion leaders or peer educators in small groups.

- Encourage use of problem-oriented decision making, clinical practice guidelines, and clinical algorithms that foster appropriate management and use of antimicrobials.

- Develop educational programmes for dispensers that enhance their understanding of appropriate and inappropriate use of antimicrobials and encourage them to educate patients regarding the importance of compliance with prescribed antibiotic regimens.

- Formulate evidence-based guidelines for relevant infections and syndromes that can be used in practice, in teaching and in monitoring adherence to recommended policies.

- If developed nationally, modify guidelines to make them relevant at the local level.

- Actively promote the use of guidelines and teaching materials to enhance their adoption.

1.4. Peer review and monitoring

- Improve provider performance and appropriate antimicrobial use by ensuring ongoing supervision of clinical practices, especially the diagnostic and treatment strategies used.

- Regularly monitor drug use practices and utilize peer comparisons or comparison with external standards to gauge performance. Feed back information regarding level of performance to individual providers.

- Link physician/prescriber licensing requirements and continued authority to prescribe to requirements for defined training and specific continuing education on antimicrobial use.

1.5. Other measures

- Identify and eliminate economic incentives (i.e. reimbursement practices) that encourage inappropriate antimicrobial use.

- Encourage the development and use of essential drug lists and formularies relevant to each practice setting.

- Control antimicrobial use by restrictive formularies that limit prescription to selected agents. Such formularies must provide appropriate antimicrobial choices, however, and must be appropriate for the level/place of care.

- Consider holding selected newer antimicrobials in ‘reserve’ at certain levels of care in order to slow the development of resistance to these newer agents.

- Consider further limiting access to antimicrobials by restricting prescribing authority to selected categories of health care worker.

2. Patients and the general public

2.1. Principles of public/patient interventions.

- Educate patients regarding the inappropriate and appropriate uses of antibiotics.
- Modify patient expectations as to when antibiotics should be used in conjunction with the above.
- Empower patients to participate in optimal medical decision making.
- Utilize behaviour change theory to most effectively modify patient behaviour with respect to antimicrobials.

2.2. Levels of Intervention

- Employ marketing skills and approaches to achieve these ends.
- Focus initially on specific target groups where antimicrobial misuse may be high (i.e. mothers of young children).
- Improve communication skills of providers to teach the above messages; motivate providers to deliver the message.
- Foster interest and participation in patient education by all relevant involved parties, including government, industry, NGOs and CBOs, professional associations, foundations, health care institutions/centres and individual providers.
- Develop levels of intervention, consistent with the above, that are international, national, local and institutional and individual.

2.3. Adherence to antimicrobial regimens

- Educate patients regarding the importance of adherence to prescribed antimicrobial regimens and the consequences of partial or intermittent therapy.
- Encourage the use of medical strategies that foster adherence (simplified and shorter regimens, directly observed therapy, blister packaging, special calendars, fixed dose combinations) and the like.

- Discourage patient self initiation and use of antimicrobials.

3. Governments & health systems

The following recommendations include actions by WHO, by national governments and their respective departments of health, and by health professionals who are involved in advising on health care.

3.1. Global advocacy of antimicrobial resistance

- Target WHO-coordinated advocacy for action towards relevant international organisations (*eg*. WTO, WB, IMF).

3.2. Legal framework

- Adapt for national use an internationally-applicable WHO-developed model legal framework for tightening and aligning legislation surrounding the licensure, manufacture, sale, supply, distribution and promotion of medicinal products.

- Adapt to the national situation a WHO-developed framework for the enforcement of all legislation which relates to these matters.

- Introduce legal requirements for the collection of data on antimicrobials which relate to production, distribution, sales and consumption in all spheres of antimicrobial use (human, veterinary, agricultural).

- Introduce formal training and registration schemes such that drugs may be distributed only to nationally recognized and certified dispensing outlets (*eg*. *via* registered pharmacies in hospitals and the community staffed by qualified personnel and *via* dispensing health professionals).

3.3. National Policies

- Make the containment of antimicrobial resistance a national priority.

- Adapt, and apply as possible, a WHO-derived model system for antimicrobial resistance surveillance. By this means, contribute to the global database.

- Create Intersectoral Task Forces (ITFs), with memberships which encompass health professionals, pharmaceutical manufacturers, government, media representatives and consumers.

- Use ITFs to raise awareness of antimicrobial resistance, to organize the collection and assimilation of data on manufacturing, distribution, sales, consumption, and resistance, and to oversee the creation of local task forces.

- Allocate resources for specific activities, including research.

- Implement public health and institutional hygiene measures aimed at the prevention of the spread of infections, and thereby the spread of resistant pathogens.

- Establish Essential Drugs Lists (EDL) and Essential Drugs Policies (EDPs) to improve the availability and use of essential drugs; these could be based on the WHO Model List of Essential Drugs.

- Maximize the effectiveness of an EDL by introducing supportive educational programmes and follow-ups.

- Establish National Standard Treatment Guidelines in connection with the EDL, with further modification for local hospital use. Support such interventions with training and supervision.

4. Hospital

4.1. Control of antimicrobial use

- Establish an effective Hospital Therapeutics Committee within each hospital, with formal links to the Infection Control Committee (ICC).

- Implement an antibiotic utilization review programme based on written guidelines for appropriate treatment and prophylaxis of infections. The programme should be locally developed with wide input and consensus and should utilize local surveillance data whenever possible.

- Utilize regular audits to provide practitioners with feedback on their antibiotic practices.

- Restrict access of industry sales representatives within the hospital environment.

- Integrate to the extent possible the activities of the hospital therapeutics committee, the infection control committee, the microbiology laboratory, and infectious disease specialists with respect to control of antimicrobial use.

4.2. Infection control committee (ICC)

- Establish an effective (adequately staffed and trained) infection control programme within the hospital.

- Ensure that essential components of the ICC include active surveillance of infection, identification of outbreaks, and implementation of effective control measures such as barrier precautions (handwashing, gloving, gowning, isolation) and sterilization and disinfection of equipment and supplies.

4.3. Laboratory factors

- Ensure that hospital laboratories can perform appropriate diagnostic testing and reproducible antimicrobial susceptibility testing of key organisms.

- Analyze laboratory data to produce surveillance reports for clinicians of patterns of antimicrobial resistance among common pathogens.

- Identify and control outbreaks of infection due to antimicrobial-resistant organisms.

- Utilize the hospital laboratory to undertake specialized microbiological testing as needed to support epidemiological investigations of hospital or community outbreaks of infection.

5. Pharmaceutical industry

The following recommendations for action are directed to governments and their health departments, to Licensing Authorities, and/or to the pharmaceutical industry itself:

5.1. The legal classification of antimicrobial agents

- Limit the legal classification of antimicrobials to prescription only medicines (POM) wherever possible within the framework of individual national health provision systems.

- Link the POM category to regulations controlling sales, supply and dispensing of medicines and to the scope of allowable promotional activities.

5.2. Control of promotional activities with the aim of reducing the inappropriate use of antimicrobials

- Align all aspects of the promotion of antimicrobials within an internationally-agreed *Code of Practice*; this could be broadly based on the existing Code of Practice produced by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

- Adapt this internationally-agreed standard to develop country-specific codes in accordance with national regulations.

- Institute systems for the monitoring of compliance with legislation on promotional activities and with relevant voluntary codes of practice.

- Apply a *regulatory pyramid* to the framework of control of promotional activities, based on interventions which are easy for regulators and the regulated to implement but with scope for increasing regulatory intervention as the degree of contravention of accepted practice increases.

- Subcontract some of the responsibility for monitoring of compliance to Non-Governmental Organizations (NGOs) in situations where the Licensing Authority itself is not able to carry out this function comprehensively.

- Work with professional medical associations to limit the scope of inducements (*eg*. event tickets, hospitality, travel and direct payments) to health professionals to prescribe antimicrobial agents regardless of clinical need.

5.3. Drug promotion to prescribers and patients

- Educate prescribers regarding the evidence that promotional activities and inducements may markedly influence their prescribing habits.

- Make prescribers aware that promotion by companies in strict accordance with a datasheet may not necessarily constitute prudent use of antimicrobials.

- Ensure that prescribers have access to approved prescribing information on individual drugs and provide impartial sources of information on the relative benefits and risks of antimicrobial therapy such that prescribers do not have to rely solely on the information (*eg*. detail aids) presented by company representatives.

- Draw up a code of practice specific to the control of direct-to-consumer advertising of POM preparations in countries where this is allowed.

- Educate patients regarding the appropriate use of antimicrobials, and the role of symptomatic relief medications for milder infections, in order to

counteract the potentially adverse influence of direct-to-consumer advertisements.

5.4. New drug discovery and development

- Encourage co-operative discovery efforts between industry and academia (public-private partnerships) with respect to new drugs and other modalities of preventing and managing infection.

- Introduce joint funding arrangement schemes between government grant-giving bodies and industry to support fundamental research programmes.

- Provide incentive schemes to companies to invest in research and development so that they do not have to rely on sales alone to recoup their R&D costs. Identify funding sources for such programmes.

- Amend and align international patent laws as necessary to provide better protection of intellectual property rights; consider extension of patents for truly innovative medicines.

- Make available and agree on qualifying criteria for fast-track schemes for obtaining marketing authorisation for novel agents.

5.5. Availability of essential drugs

- Encourage co-operation between governments, health care delivery systems and the pharmaceutical industry to improve the availability of essential drugs in all countries.

- Consider incentive schemes along the lines mentioned above which might facilitate such co-operative efforts.

6. Non-human uses of antimicrobials

- Develop and facilitate implementation of global guidelines for containment of antimicrobial resistance from use of antimicrobials in livestock to reduce the risk for selection and dissemination of antimicrobial resistance to humans. This should include production, licensing, distribution, sales and use of antimicrobials and should facilitate close coordination between authorities licensing drugs for animals and humans

- Growth promoters which select for resistance to antimicrobial agents used for human treatment should not be used in animal husbandry

- Ensure that education of prescribers and farmers should include prudent use of antimicrobials in animal husbandry and the risks of selecting resistant bacteria in food-producing animals.

- Develop and implement standards of practice to ensure that antimicrobial agents are not used as a substitute for adequate hygiene in animal husbandry.

- Encourage the development of production practices to reduce antimicrobial use in food animals. This may include animal health-oriented management systems and disease prevention measures to make the best possible use of the genetic potential for animal performance, and utilization of alternatives to antimicrobial agents for infectious disease prevention and control, such as vaccines and probiotics.

- Ascertain and monitor the prevalence of resistant bacteria in food-producing animal populations and animal-based food products. The antimicrobial resistance monitoring programme must allow for correlating with similar data from human isolates. Collaboration of the medical, veterinary and agricultural sectors is vitally important due to the wide variety of laboratories and logistics involved in sample procurement and transport. Joint working groups at national level, including researchers and decision makers from all involved sites, should be established, agree working plans and coordinate activities. Surveillance of antimicrobial resistance serves as an important tool to develop guidelines for antibiotic use for practising veterinarians.

- Establish programmes for monitoring the consumption of antimicrobials by food animals to identify misuse and trigger investigations for identification of factors leading to overprescribing or other forms of misuse. Quantitative data on the use of antimicrobials are essential for assessment of the association between drug use and the selection and spread of resistance. Such data should be available to the appropriate authority.

D. Knowledge gaps & research needs

The knowledge gaps and research needs listed below were presented by the rapporteurs of each working group and further items were extracted from the written text provided by each of the groups.

1. Prescriber behaviour

1.1 How can policies be translated into practice in a sustained manner to improve: a) clinical diagnosis and disease management; b) prescribing practices (antimicrobial use patterns); c) patient care practices (handwashing, catheter insertion, etc.); d) adverse effects monitoring and reduction.

1.2 What are the most appropriate and cost-effective training strategies to achieve the above?

1.3 Do these practices result in improved antimicrobial use and infection control and in reduction in the emergence and spread of antimicrobial resistance?

2. Patient/public behaviour

2.1 Why are certain antimicrobials so popular; for example, injections rather than oral formulations; why some particular products rather than others (e.g. capsule rather than tablet; some colours rather than others)?

2.2 What factors influence patients' expectations from antimicrobials?

2.3 What satisfies a patient in lieu of a prescription for an antimicrobial at every consultation?

2.4 What is the impact of gender on antimicrobial use?

2.5 In what circumstances do large and small group campaigns (designed to reduce antimicrobial use) lead to behavioural change?

2.6 Can health educators employ better marketing techniques?

2.7 What patient educational materials and other supportive tools impact optimally on patient behaviour (with respect to antimicrobial use)?

3. Laws and regulations

3.1 What would be the impact on antimicrobial resistance of enforcement of existing laws and regulations?

3.2. What are the effects of health sector reform and health care policy with respect to antimicrobial use and antimicrobial resistance?

3.3 Do economic and regulatory strategies have an impact on changing prescribers' behaviour?

3.4 What are the effects of reimbursement, patient charges, and health insurance on antimicrobial resistance? For example, a) is there an impact on these on inappropriate antimicrobial use?; b) to what extent does a patient's economic situation lead to overuse of antimicrobial?; c) do cost control policies have an impact on inappropriate antimicrobial use prescribing?

3.5 Are the effects of rigid formularies, antimicrobial use approval and treatment guidelines positive or negative with respect to antimicrobial resistance?

4. Pharmaceutical industry: promotional activities and research and development

4.1 How can key information on safety and efficacy of antimicrobials best be presented so that it is retained by the target audience?

4.2 What are the effects (positive and negative) of medical representatives of drug companies and industry incentives in general (advertising, seminars, travel, free lunches, etc) on the problem of antimicrobial resistance?

4.3 What incentives are needed for pharmaceutical companies to expand research in discovery of new molecular entities and new modalities of preventing and managing infection (such as vaccines and immune modulators) that will provide new, affordable treatments in the future?

4.4 What criteria/data can be used to predict, at an early stage of drug development, the dosage regimens that should be explored in major clinical trials to minimize the risk of selecting resistance while achieving favourable outcome ? [licensing authorities should consider requiring that such investigations are carried out as part of the drug development process]?

4.5 Can clinical trial protocols be designed so that the role of resistance in determining clinical and microbiological outcome can be assessed?

4.6 What incentives are needed for companies to expand research into improved rapid diagnostics for infections, including simple, affordable, field-adapted diagnostics?

5. Pharmacological and clinical issues

5.1 What are the most appropriate pharmacokinetic and pharmacodynamic factors which determine the maximum efficacy and minimum emergence of resistance for an antimicrobial? (require disease- and antimicrobial-specific studies).

5.2 What is the dose and duration of therapy that maximizes efficacy and minimizes emergence of resistance (Will require disease- and antimicrobial-specific studies; resistance should be included in evaluation of the outcome).

5.3 What is the effect of patient adherence to prescribed therapy on emergence of resistance?

5.4 What is the impact of oral versus injectable therapy on resistance?

5.5 What are the effects of combination antimicrobial therapy on resistance (and on efficacy)?

5.6 What are the effects of antimicrobials with long half-lives on the development of resistance both in pathogens and in the normal flora?

5.7 Does inferior drug quality impact the selection of resistance?

5.8 What are the clinical implications of resistance detected in vitro (must be assessed by specific site and pathogen)?

5.9 What is the impact of interventions that are designed to change antimicrobial use on patient outcome? For example:

a) How do symptom scores and patient satisfaction compare when respiratory infections (e.g. purulent rhinitis/common cold or cough/bronchitis) are treated with symptomatic therapy, antimicrobials or placebo?

b) What is the impact of deferring antimicrobial therapy for acute otitis media? (since up to 80% of infections will resolve within 2-3 days without antimicrobial therapy).

c) Do case management criteria for fever and rash in non-malarious areas (e.g. incorporated into guidelines for the integrated management of childhood illnesses) improve antimicrobial use?

6. Microbial genetics and ecology

6.1 What is the biological price in terms of reduced virulence that microorganisms pay for antimicrobial resistance?

6.2 What is the impact of antimicrobial cycling on this biological price?

6.3 Why do some antimicrobials have a greater tendency to select for resistance than others (both within and between antimicrobial classes)?

6.4 What are the clinical implications and other effects of cross resistance?

6.5 How do the antimicrobial concentrations in phagocytes impact the selection of resistance?

6.6 What are the links and interactions between antimicrobial resistance in hospitals, nursing homes and the community?

6.7 What is the impact of vaccines on the problem of antimicrobial resistance in general and on the carriage of resistant strains (specifically serotypes)?

7. Detection and surveillance of resistance

7.1 What are the essential quality assurance procedures required to ensure meaningful antimicrobial resistance data?

7.2 What is the role and cost-effectiveness of culture and antimicrobial susceptibility testing in specific patient care circumstances (including managed care settings)?

7.3 Can rapid methods, applicable to international surveillance systems, be developed to identify resistant bacteria?

7.4 What are the key surveillance networks for combating antimicrobial resistance?

8. Non-human uses of antimicrobials

Many of the above-mentioned knowledge gaps and research needs related to prescribers' behaviour, effects and enforcement of laws and regulations, results of pharmaceutical industry promotional activities, and detection and surveillance of resistance are also valid for non-human use of antimicrobials.

8.1 Clinical trials to optimize dose, dose interval and duration of antimicrobial treatment in animals to improve prescription use of antimicrobials;

8.2 Prevention and control of foodborne and zoonotic diseases at the animal production level to reduce the risk of transmission of resistant bacteria to humans;

8.3 Non-antimicrobial alternatives for the control of infectious diseases and syndromes in animals, particularly multifactorial diseases in young animals;

8.4 Development of more rapid diagnostic methods for bacterial infections to reduce need for empirical treatment;

8.5 Interspecies transfer of antimicrobial resistance (plant, animal, humans, environmental organisms);

8.6 Rate of development of medically important bacterial resistance in food-producing animals, in relation to duration of exposure to and concentration of antimicrobial (especially concentrations below the MIC) and including the resistance selection potential of antimicrobials at permitted minimum residue levels;

8.7 Effect of cessation of use of specific antimicrobials on the prevalence and persistence of resistant bacterial in food-producing animals and their immediate environment;

8.8 Means to re-establish the normal antimicrobially susceptible flora following antimicrobial usage;

8.9 Information on the stability of important antimicrobials and their metabolites in the environment;

8.10 Impact of the use of antimicrobials in domestic pets and birds on the development and persistence of resistance bacteria in the farm environment;

8.11 Alternative approaches for growth promotion that do not require antimicrobials;

8.12 Risks from the presence of resistance genes in bacteria used as probiotics;

8.13 Appropriate risk assessment models and data needed to allow the models to be implemented;

8.14 Appropriate post-approval monitoring schemes to complement pre-approval risk assessment models.

ANNEX 1

REFERENCES

1. Prescribers and dispensers

Ameyaw MM, Ofori-Adjei D. The impact of three forms of educational interventions on dispensing practices. Presented at ICIUM Chang Mai 1997. http://www.who.int/dap-icium/posters/2b1_txt1.html

Avorn J, Soumerai SB. Improving drug-therapy decisions through educational outreach. *New England Journal of Medicine* 1983;308:1457-1463.

Bauchner H. Parent's impact on antibiotic use. *APUA Newsletter* 1997;15:1-3.

Bosu WK, Ofori-Adjei D. Survey of antibiotic prescribing pattern in government health facilities of the Wassa west district of Ghana. *East African Medical Journal* 1997;74:138-142.

Bruneton C, Maritoux J, Fontaine D. Assessment in 7 African countries of the advice given in private drugstores through local researchers role playing customers. Presented at ICIUM Chang Mai 1997. http://www.who.int/dap-icium/posters/1b2_fin.html

Butler CC, Rollnick S, Pill R, Maggs-Rapport F, Stott N. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *British Journal of Medicine* 1998;317:637-642.

Chalker J, Phuong NK. Combating the growth of resistance to antibiotics. Presented at ICIUM Chang Mai 1997. http://www.who.int/dap-icium/posters/2E1_txtf.html

Coast J, Smith RD, and Millar MR. An economic perspective on policy to reduce antimicrobial resistance. *Social Science and Medicine* 1998;46:29-38.

Cockburn J, Reid AL, Bowman JA, Sanson-Fisher RW. Effects of intervention on antibiotic compliance in patients in general practice. *Medical Journal of Australia* 1987;147:324-328.

De Vries TPGM, Henning RH, Hogerzeil HV, Bapna JS, Bero L, Kafle KK, Mabadeje AFB, Santoso B, Smith AJ. Impact of short course in pharmacotherapy for undergraduate medical students. *Lancet* 1995;346:1454-1457.

Annex 1

De Vries TPGM, Henning RH, Hogerzeil HV, Fresle DA. Guide to good prescribing. Geneva: World Health Organization, 1994 *WHO/DAP/94.11* (in English and French)

Drusano GL. Infection in the intensive care unit: B-lactamase-mediated resistance among enterbacteriaceae and optimal antimicrobial dosing. *Clinical Infectious Diseases* 1998;27(suppl 1):S111-S116.

Fidler DP. Legal Issues Associated with Antimicrobial drug resistance. Emerging Infectious Diseases 4: 1998

Gani L, Tangkilisan A, Pujilestari L. Improving rational prescribing of physicians: an educational approach for acute diarrhoea in children in Jakarta. Presented at ICIUM Chang Mai 1997. http://www.who.int/dap-icium/posters/2b2_text.html

Goldmann DA, Huskins WC. Control of nosocomial antimicrobial resistant bacteria: a strategic priority for hospitals worldwide. *Clinical Infectious Diseases* 1997;24(suppl 1):S139-S145.

Guillermot D, Carbon C, Balkau B, Geslin P, Lecoeur H, Vauzelle-Kervroeden A, Bouvenot G, Eschwege E. Low dosage and long treatment duration of B-lactam. Risk factors for carriage of penicillin-resistant Streptococcus pneumoniae. *Journal of the American Medical Association* 1998;279:365-370.

Gumodoka B, Vos J, Berege ZA, van Asten HA, Dolmans WM, Borgdorff MW. Injection practices in Mwanza region, Tanzania: prescriptions, patient demand and sterility. *Tropical Medicine and International Health* 1996;1:874-880.

Harvey KJ, Stewart R, Hemming M, Naismith N, Moulds RFW. Educational antibiotic advertising. *Medical Journal of Australia* 1986;145:28-32.

Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. *American Journal of Medicine* 1989;87:540-546.

Hogerzeil HV, Bimo, Ross-Degnan D, Laing RO, Ofori-Adjei D, Santoso B, Azad Chowdhury AK, Das AM, Kafle KK, Mabadeje AFB, Massele AY. Field tests for rational drug use in twelve developing countries. *Lancet* 1993;342:1408-1410.

Hossain MM, Glass RI, Khan MR. Antibiotic use in a rural community in Bangladesh. *International Journal of Epidemiology* 1982;11:402-405.

Annex 1

Hui L, Li XS, Zeng XJ, Dai YH, Foy HM. Patterns and determinants of use of antibiotics for acute respiratory tract infection in children in China. *Pediatric Infectious Disease Journal* 1997;16:560-564.

Kristinsson KG. Epidemiology of penicillin resistant pneumococci in Iceland. *Microbial Drug Resistance* 1995;1:121-125.

Kunin CM, Lipton HL, Tupasi T, Sacks T, Scheckler WE, Jivani A, Goic A, Martin RR, Guerrant RL, Thamlikitkul V. Social, behavioral, and practical factors affecting antibiotic use worldwide: report of task force 4. *Reviews of Infectious Diseases* 1987;9 (suppl 3):S270-S284.

Little P, Williamson I, Warner G, Gould C, Gantly M, Kinmonth AL. Open randomized trial of prescribing strategies in managing sore throat. *British Medical Journal* 1997;314:722-727.

Loulergue J, Audurier A, DeLarbre JM, De Gialluly C. Changes in microbial ecology and use of cloxacillin. *Journal of Hospital Infection* 1994;27:275-283.

Mabadeje AFB, Taylor O, Abiose AK. Intervention study to reduce prescription cost in the Lagos University Teaching Hospital. Presented at ICIUM Chang Mai 1997. http://www.who.int/dap-icium/posters/2a3_txt.html

Macfarlane J, Holmes W, Macfarlane R. Reducing reconsultations for acute lower respiratory tract illness with an information leaflet: a randomized controlled study of patients in primary care. *British Journal of General Practice* 1997;47:719-722.

Macfarlane J, Holmes W, Macfarlane R, Britten N. Influence of patients' expectations of antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *British Medical Journal* 1997;315:1211-1214.

Mamun KZ. Prevalence and genetics of resistance to commonly used antimicrobial agents in faecal enterbacteriaceae from children in Bangladesh. PhD Thesis, University of Liverpool, 1991.

Milatovic D, Braveny I. Development of resistance during antibiotic therapy. *European Journal of Clinical Microbiology*. 1987;6:234-44.

Molstad S, Ekedahl A, Hovelius B, Thimansson H. Antibiotics prescription in primary care: a 5-year follow-up of an educational programme. *Family Practice* 1994;11:282-286.

Annex 1

Norrby SR. Antibiotic resistance: a self-inflicted problem. *Journal of Internal Medicine* 1996;239:373-375.

Pichichero ME, Cohen R. Shortened course of antibiotic therapy for acute otitis media, sinusitis and tonsillopharyngitis. *Pediatric Infectious Diseases Journal* 1997;16:680-95.

Rice LB, Willey SH, Papanicolaou GA, Medeiros AA, Eliopoulos GM, Moellering RC Jr. Outbreak of ceftazidime resistance caused by extended-spectrum beta-lactamases at a Massachusetts chronic-care facility. *Antimicrobial Agents and Chemotherapy* 1990;34(1):2193-2199.

Schentag JJ, Hyatt JM, Carr JR, Paladino JA, Birmingham MC, Zimmer GS, Cumbo TJ. Genesis of methicillin-resistant *Staphylococcus aureus* (MRSA), how treatment of MRSA infections has selected for vancomycin-resistant *Enterococcus faecium*, and the importance of antibiotic management and infection control. *Clinical Infectious Diseases* 1998;26:1204-1214.

Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, Huovinen P, The Finnish Study Group for Antimicrobial Resistance. The effect of changes in the consumption of macrolide antibiotics of erythromycin resistance in group A streptococci in Finland. *New England Journal of Medicine* 1997;337:441-446.

Sia IC, Valerio J. The effects of an intervention on the selling behaviour of sarisari (variety) store keepeers in some villages in the Philippines. Presented at ICIUM Chang Mai 1997. http://www.who.int/dap-icium/posters/3C4_TXTF.html

Soumerai SB, McLaughlin T, Avorn J. Improving drug prescribing in primary care: a critical analysis of the experimental literature. *Milbank Quarterly* 1989;67:268-317.

Thomas JK, Forrest A, Bhavnani SM, Hyatt JM, Cheng A, Ballow CH, Schentag JJ. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. *Antimicrobial Agents and Chemotherapy* 1998,42(3):521-527.

Tomasz A. Multiple-antibiotic-resistant pathogenic bacteria: a report on the Rockefeller University Workshop. *New England Journal of Medicine* 1994;330:1247-1251.

UK Department of Health. Standing Medical Advisory Committee, Sub-Group on Antimicrobial resistance. Main report: The path of least resistance, London, UK Department of Health September 1998.

World Health Organization. How to investigate drug use in health facilities. 1993 *WHO/DAP/93.1*.

Yu VL, Stoehr GP, Starling RC, Shogan JE. Empiric antibiotic selection by physicians: evaluation of reasoning strategies. *American Journal of Medical Sciences* 1991,301:165-172.

2. Patients: the public

Bloom BR, Murray CJL. Tuberculosis: commentary on a reemergent killer. *Science* 1992;257:1055-1064.

Branthwaite A, Pechere JC. Pan-European survey of patients' attitudes to antibiotics and antibiotic use. *Journal of International Medical Research* 1996;24:229-238.

Buckalew LW, SallisRE. Patient compliance and medication perception. *Journal of Clinical Psychology* 1986;42:49-53.

Cockburn J, Reid AL, Bowman JA, Sanson-Fisher RW. Effects of intervention on antibiotic compliance in patients in general practice. *Medical Journal of Australia* 1987;147:324-328.

Couper MR. Strategies for the rational use of antimicrobials. *Clinical Infectious Diseases* 1997;24(suppl 1):S154-S156.

Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City – turning the tide. *New England Journal of Medicine* 1995;333:229-233.

Haak H. Pharmaceuticals in two Brazilian villages: lay practices and perceptions. *Social Science and Medicine* 1988;27:1415-1427.

Kunin CM, Lipton HL, Tupasi T, Sacks T, Scheckler WE, Jivani A, Goic A, Martin RR, Guerrant RL, Thamlikitkul V. Social, behavioral, and practical factors affecting antibiotic use worldwide: report of task force 4. *Reviews of Infectious Diseases* 1987;9 (suppl 3):S270-S284.

Annex 1

Lipsky MS, Taylor CA. The opinions and experiences of family physicians regarding direct-to-consumer advertising. *Journal of Family Practice* 1997;45:495-499.

Macfarlane J, Holmes W, Macfarlane R. Reducing reconsultations for acute lower respiratory tract illness with an information leaflet: a randomized controlled study of patients in primary care. *British Journal of General Practice* 1997;47:719-722.

Macfarlane J, Holmes W, Macfarlane R, Britten N. Influence of patients' expectations of antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *British Medical Journal* 1997;315:1211-1214.

Morris LA, Brinberg D, Klimberg R, Rivera C, Millstein LG. Attitudes of consumers towards direct advertising of prescription drugs. *Public Health Reports* 1986;101:82-89.

Nichter M, Vuckovic N. Agenda for an anthropology of pharmaceutical practice. *Social Science and Medicine* 1994;39:1509-1525.

Paredes P, Yeager BAC, Montalvo J, Arana A. Intervention trial to decrease unjustified use of pharmaceuticals drugs in the treatment of childhood diarrhea, Lima, Peru. Presented at ICIUM Chang Mai 1997. http://www.who.int/dap-icium/posters/3A2_TEXT.html

Querubin MP, Tan ML. Old roles, new roles: women, primary health care, and pharmaceuticals in the Philippines. In: *Adverse Effects: Women and the Pharmaceutical Industry.* Women's Educations Press/International Organization of Consumers' Unions, Toronto, 1986.

Sackett D, Snow JC. The magnitude of compliance and non-compliance. In *Compliance in Health Care*. Eds Haynes RB, Taylor DW, Sackett D. John Hopkins, Baltimore, 1979.

Shapiro MF. Regulating pharmaceutical advertising: what will work? *Canadian Medical Association Journal* 1997;156:359-361.

Sharpe TR, Mikeal RL. Patient compliance with antibiotic regimens. *American Journal of Hospital Pharmacists* 1974;31:479-484.

Annex 1

'T Hoen E. Direct-to-consumer advertising: for better profits or for better health? *American Journal of Health Systems Pharmacists* 1998;55:594-597.

Trostle JA. Medical compliance as an ideology. *Social Science and Medicine* 1988;27:1299-1308.

UK Department of Health. Standing Medical Advisory Committee, Sub-Group on Antimicrobial resistance. Main report: The path of least resistance, London, UK Department of Health September 1998.

Vuckovic N, Nichter M. Changing patterns of pharmaceutical practice in the United States. *Social Science and Medicine* 1997;44:1285-1302.

Weis SE, Slocum PC, Blais FX, King B, Nunn M, Matney B, Gomez E, Foresman BH. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *New England Journal of Medicine* 1994;330:1179-1184.

World Health Organization. Public education in rational drug use. 1994 *WHO/DAP/94.1*.

World Health Organization. Rational drug use: consumer education and information. 1996 *DAP/MAC/(8)96.6.*

3. Governments and health systems

Bosu WK, Ofori-Adjei D. Survey of antibiotic prescribing pattern in government health facilities of the Wassa west district of Ghana. *East African Medical Journal* 1997;74:138-142.

Haak H. Pharmaceuticals in two Brazilian villages: lay practices and perceptions. *Social Science and Medicine* 1988;27:1415-1427.

Hart CA, Kariuki S. Antimicrobial resistance in developing countries. *British Medical Journal* 1998;317:647-650.

Hogerzeil HV. Promoting rational prescribing: an international perspective. *British Journal of Clinical Pharmacology* 1995;39:1-6.

Annex 1

Hogerzeil HV, Walker GJA, Sallami AO, Fernando G. Impact of an essential drug programme on the availability and rational use of drugs. *Lancet* 1989;21 Jan:141-142.

Hossain MM, Glass RI, Khan MR. Antibiotic use in a rural community in Bangladesh. *International Journal of Epidemiology* 1982;11:402-405.

Hui L, Li XS, Zeng XJ, Dai YH, Foy HM. Patterns and determinants of use of antibiotics for acute respiratory tract infection in children in China. *Pediatric Infectious Disease Journal* 1997;16:560-564.

Indalo AA. Antibiotic sale behaviour in Nairobi: a contributing factor to antimicrobial drug resistance. *East African Medical Journal* 1997;74(3):171-173.

Kafuko JM, Zirabamuzaale C, Bagenda D. Rational drug use in rural health units of Uganda: effect of national standard treatment guidelines on rational drug use. Presented at ICIUM Chang Mai 1997. http://www.who.int/dap-icium/posters/2f3_text.html

Levy SB, Burke JP, Wallace CK. Epilogue. *Reviews of Infectious Diseases* 1987;9(suppl 3):S313-316.

Lindtjorn B. Essential drugs list in a rural hospital. Does it have any influence on drug prescription. *Tropical Doctor* 1987;17(4):151-155.

National Drug Committee. Ghana Ministry of Health. Master Plan for the Ghana National Drugs Programme (GNDP) 1995-1999. Accra, December 1994.

UK Department of Health. Standing Medical Advisory Committee, Sub-Group on Antimicrobial resistance. Main report: The path of least resistance, London, UK Department of Health September 1998.

World Health Organization. Counterfeit drugs: report of a joint WHO/IFPMA workshop. 1992 *WHO/DMP/CFD/92*.

Annex 1

4. Hospitals

Acar JF, Goldstein FW. Consequences of increasing resistance to antimicrobial agents. *Clinical Infectious Diseases* 1998;27(suppl 1):S125-S130.

Albert RK, Condie F. Hand-washing patterns in medical intensive-care units. *New England Journal of Medicine* 1981;304:1465-1466.

Aswapokee N, Vaithayapichet S, Komoltri C. The failure of a pre-printed order form to alter physicians antimicrobial prescribing patterns. *Journal of Medical Association of Thailand* 1992;75:223-230.

Avorn J, Soumerai SB, Taylor W, Wessels MR, Janousek J, Weiner M. Reduction of incorrect antibiotic dosing thorough a structured educational order form. *Archives of Internal Medicine* 1988;148:1720-1724.

Ayliffe GAJ. The progressive intercontinental spread of methicillin-resistant *Staphylococcus aureus*. *Clinical Infectious Diseases* 1997;24(suppl 1):S74-79.

Barber M, Dutton AAC, Beard MA, Elmes PC, Williams R. Reversal of antibiotic resistance in hospital staphylococcal infection. *British Medical Journal* 1960;1:11-17.

Betts RF, Valenti WM, Chapman SW, Chonmaitree T, Mowrer G, Pincus P, Messner M, Nessner M, Robertson R. Five-year surveillance of aminoglycoside usage in a university hospital. *Annals of Internal Medicine* 1984;100:219-222.

Bonhoeffer S, Lipsitch M, Levin BR. Evaluating treatment protocols to prevent antibiotic resistance. *Proceedings of the National Academy of Science* 1997;94:12106-12111.

Giamarellou H, Antoniadou A. The effect of monitoring of antibiotic use on decreasing antibiotic resistance in the hospital. In: Antibiotic resistance: origins, evolution, selection and spread. Wiley, Chichester (Ciba Foundation Symposium 207) 1997:76-92.

Goldmann DA, Huskins WC. Control of nosocomial antimicrobial resistant bacteria: a strategic priority for hospitals worldwide. *Clinical Infectious Diseases* 1997;24(suppl 1):S139-S145.

Annex 1

Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, Schlosser J, Martone WJ, for the workshop to prevent and control the emergence and spread of antimicrobial-resistant microorgamisms in hospitals. Strategies to prevent and control the emergence and spread of antimicrobial resistant microorganisms in hospitals: a challenge to hospital leadership. *Journal of the American Medical Association* 1996;275:234-240.

Graham M. Frequency and duration of handwashing in an intensive care unit. *American Journal of Infection Control* 1990;18:77-81.

Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet* 1993;342:1317-1322.

Gumodoka B, Vos J, Berege ZA, van Asten HA, Dolmans WM, Borgdorff MW. Injection practices in Mwanza region, Tanzania: prescriptions, patient demand and sterility. *Tropical Medicine and International Health* 1996;1:874-880.

Gyssens IC, Blok WL, van den Broek PJ, Hekster YA, van der Meer JWM. Implementation of an educational program and an antibiotic order form to optimize quality of antimicrobial drug use in a department of internal medicine. *European Journal of Clinical Microbial Infectious Diseases* 1997;16:904-912.

Hogerzeil HV. Promoting rational prescribing: an international perspective. *British Journal of Clinical Pharmacology* 1995;39:1-6.

Hughes JM, Tenover FC. Approaches to limiting emergence of antimicrobial resistance in bacteria in human populations. *Clinical Infectious Diseases* 1997;24(suppl 1):S131-S135.

Larson E, Kretzer EK. Compliance with handwashing and barrier precautions. *Journal of Hospital Infection* 1995;30(suppl):88-106.

Levy SB, Burke JP, Wallace CK. Epilogue. *Reviews of Infectious Diseases* 1987;9(suppl 3):S313-316.

Mayer JA, Dubbert PM, Miller M, Burkett PA, Chapman SW. Increasing handwashing in an intensive care unit. *Infection Control* 1986;7:259-262.

Pestotnik SL, Classen DC, Evans RS, Burke JP. Implementing antibiotic practice guidelines through computer-assisted decision support: clinical and financial outcomes. *Annals of Internal Medicine* 1996;124:884-890.

Recco RA, Gladstone JL, Friedman SA, Gerken EH. Antibiotic control in a municipal hospital. *Journal of the American Medical Association* 1979;241:2283-2286.

Annex 1

Rifenburg RP, Paladino JA, Hanson SC, Tuttle JA, Schentag JJ. Benchmark analysis of strategies hospitals use to control antimicrobial expenditures. *American Journal of Health Systems Pharmacists* 1996;53:2054-2062.

Riley LW, Ceballos BSO, Trabulsi LR, Fernandes de Toledo MR, Blake PA. The significance of hospitals as reservoirs for endemic multiresistant *Salmonella typhimurium* causing infection in urban Brazilian children. *Journal of Infectious Diseases* 1984;150:236-241.

Schentag JJ. Understanding and managing antimicrobial resistance in institutional settings. *American Journal of Health-Systems Pharmacists* 1995;52(suppl 2):S9-S14.

Schentag JJ, Hyatt JM, Carr JR, Paladino JA, Birmingham MC, Zimmer GS, Cumbo TJ. Genesis of methicillin-resistant *Staphylococcus aureus* (MRSA), how treatment of MRSA infections has selected for vancomycin-resistant *Enterococcus faecium*, and the importance of antibiotic management and infection control. *Clinical Infectious Diseases* 1998;26:1204-1214.

Soumerai SB, Avorn J. Efficacy and cost containment in hospital pharmacotherapy: state of the art and future directions. *Milbank Memorial Fund Quarterly/Health and Society* 1984;62:447-474.

Struelens MJ. The epidemiology of antimicrobial resistance in hospital acquired infections: problems and possible solutions. *British Medical Journal* 1998;317:652-654.

UK Department of Health. Standing Medical Advisory Committee, Sub-Group on Antimicrobial resistance. Main report: The path of least resistance, London, UK Department of Health September 1998.

Urban C, Go E, Mariano N, Berger BJ, Avraham I, Rubin D, Rahal JJ. Effect of sulbactam on infections caused by imipenen-resistant *Acinetobacter calcoaceticus* biotype *anitratus*. *Journal of Infectious Diseases* 1993;167;448-451.

US Congress. Office of Technology Assessment. Impacts of antibiotic resistant bacteria, OTA-H-629. Washington, DC, US Government Printing Office, 1995.

Vos J, Gumodoka B, van Asten HA, Berege ZA, Dolmans WM, Borgdorff MW. Improved injection practices after the introduction of treatment and sterility guidelines in Tanzania. *Tropical Medicine and International Health* 1998;3:291-296.

Annex 1

Weekes LM, Brooks C. Drugs and therapeutics committees in Australia: expected and actual performance. *British Journal of Clinical Pharmacology* 1996;42:551-557.

5. Private industry

Alvero RGY, Panganiban DL. Teaching critical appraisal of medicinal drug promotions in medical school. Presented at ICIUM Chang Mai 1997. http://www.who.int/dap-icium/posters/2a1_text.html

Avorn J, Chen M, Hartley R. Scientific versus commercial sources of influence on the prescribing behavior of physicians. *American Journal of Medicine* 1982;73:4-8.

Lexchin J. Enforcement of codes governing pharmaceutical promotion: what happens when companies breach guidelines? *Canadian Medical Association Journal* 1997;156(3):351-356.

Lexchin J. Interactions between physicians and the pharmaceutical industry: what does the literature say? *Canadian Medical Association Journal* 1993;149(10):1401-1407.

Wilkes MS, Dolin BH, Shapiro MF. Pharmaceutical advertisements in leading medical journals: experts'assessments. *Annals of Internal Medicine* 1992;116:912-919.

Zarate CE, Llosa IL. Prescribing habits of Peruvian physicians and factors influencing them. *Bulletin of PAHO* 1995;29(4):328-337.

6. Non-medical uses

Aarestrup FM, Bager F, Jensen N, Madsen M, Meyling A, Wegener HC. Surveillance of antimicrobial resistance in bacteria isolated from food animals to antimicrobial growth promoters and related therapeutic agents in Denmark. *APMIS* 1998; 106: 606-622.

Anonymous 1996. The Foodborne Diseases Active Surveillance Network, 1996. *Morbidity and Mortality Weekly Report* March 28, 1997; 46 (12): 258-61.

Annex 1

Bowler I, Day D. Emerging quinolone resistance in Campylobacters. *Lancet* 1992; (340): 245.

Dial GD, Wiseman PR, Davies WE, Marsh TW, Molitor RB, Morrison RB, Thawley DG. Strategies employed in the USA for improving the health of swine. *Pig News and Information* 1992; 13(3):111-123.

Dupont, H., Stelle, J. Use of antimicrobial agents in animal feeds:implications for animal health. *Reviews of Infectious Diseases* 1987; 9(3):447-457.

Endtz HP, Ruijs GJ, van Klingeren B, Jansen WH, van der Reyden T, Mouton RP. Quinolone resistance in Campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. *Journal of Antimicrobial Chemotherapy* 1991; 27:199-208.

FEDESA, 1998. Survey of Antimicrobial Usage in Animal Health in the European Union and Switzerland. Unpublished document.

Frost JA, Kelleher A, Rowe B. Increasing ciprofloxacin resistance in salmonellas in England and Wales 1991-1994. *Journal of Antimicrobial Chemotherapy* 1996; 37: 85-91.

Glynn MK, Bopp C, Dewitt W, Dabney P, Mokhtar M, Angulo FJ. Emergence of multidrug-resistant Salmonella enterica serotype typhimurium DT104 infections in the United States. *New England Journal Medicine* 1998;338:1333-8.

Gloyd JS. Protecting your practice and the food animal industry.*Journal of the American Veterinary Medical Association* 1987;190(1):32-4

Holmberg, S. D. et al. Drug resistant Salmonella from animals fed antibiotics. *New England Journal of Medicine* 1987; 311:617-622.

Institute of Medicine. Human health risks associated with the subtherapeutic us of penicillin or thetracycline in animal feed. National Academy Press. Washington DC. 1989

Hammerum AM, Jensen LB, Aarestrup FM. Detection of the satA gene and transferability of virginiamycin resistance in Enterococcus faecium from food-animals.*FEMS Microbiology Letter* 1998;168(1):145-51.

Hummel, R., Tschape, H., and Witte, W. Spread of plasmid-mediated nourseothricin resistance in connection with antibiotic use in animal husbandry. *Journal of Basic Microbiology* 1986; 26:461-466.

Annex 1

Jakobsen BM, Skou M, Hammerum AM, Jensen, LB. In vivo transfer of the satA gene between isogenic strains of *Enterococcus faecium* in the mammalian gastrointestinal tract. In Proc. Second world congress on anaerobic bacteria and infections. Nice, France, October 3-6, 1998.

Levy, S. B., Fitzgerald, G. G. and Macone, A. B. Changes in the intestinal flora of farm personnel after introduction of tetracycline-supplemented feed on a farm. *New England Journal of Medicine* 1976; 295:583-588.

Levy, S. B. Antibiotic use for growth promotion in animals: ecology and public health consequences. *Journal of Food Protection* 1987; 50:616-620.

Marshall, B. M., Petrowski, D., and Levy, S. B. Inter and intraspecies spread of E. Coli in a farm environment in the absence of antibiotic usage. *Proceedings of the National Academy of Science* (USA) 1987; 87:6609-6613.

Molbak K, Baggesen DL, Aarestrup FM, Ebbesen JM, Engberg J, Frydendahl K, Gerner-Smidt P, Petersen AM, Wegener HC. An outbreak of multidrug-resistant, quinolone-resistant Salmonella enterica serotype typhimurium DT104. *New England Journal of Medicine* 1999;341(19):1420-5

Piddock J. Does the use of antimicrobial agent in veterinary medicine and animal husbandry select antibiotic-resistant bacteria that infect an and compromize antimicrobial chemotherapy? *Antimicrobial Chemotherapy* 1996;38:1-3.

Poppe C, Smart N, Khakhria R, Johnson W, Spika J, Prescott J. Salmonella Typhimurium DT104: a virulent and drug-resistant pathogen. *Canadian Veterinary Journal* 1998;39:559-565.

Ramos JM, Ales JM, Cuenca-Estrella M, Fernandez-Roblas R, Soriano F. Changes in susceptibility of Salmonella enteritidis, Salmonella typhimurium, and Salmonella virchow to six antimicrobial agents in a Spanish hospital, 1980-1994. *European Journal of Clinical Microbiology and Infectious Disease* 1996;15:85-8.

Ridley A, Threlfall EJ. Molecular epidemiology of antibiotic resistance genes in multiresistant epidemic Salmonella typhimurium DT 104. *Microbial Drug Resistance* 1998;4(2):113-8

Ryan, C. A., Nickels, M. K. et al. Massive outbreak of antimicrobial-resistant salmonellosis traced to pasteurized milk. *Journal of the American Medical Association* 1987;258:3269-3279.

Annex 1

Sanchez R, Fernandez-Baca V, Diaz MD, Munoz P, Rodriguez-Creixems M, Bouza E. Evolution of susceptibilities of Campylobacter spp. to quinolones and macrolides. *Antimicrobial Agents Chemotherapy* 1994;38:1879-82.

Smith KE, Bessel JM, Hedberg CW, et al. Quinolone-resistant Campylobacter jejuni infections in Minnesota, 1992-1998. *New England Journal of Medicine* 1999;340:1525-32.

Stöhr, K.. (1995): Impact of Zoonotic Salmonella on Public Health and Economics. *Southeast Asian.Journal of Tropical Medicine and Public Health*, 26, Suppl. 2, 7-13

Tauxe RV. Salmonella: A postmodern pathogen. *Journal of Food Protection*. 1991; 54(7):563-568.

Tee W, MijchA, Wright E, Jung A. Emergence of multidrug resistance in Campylobacter jejuni isolates from 3 patients infected with human immunodeficiency virus. *Clinical Infectious Diseases*. 1995; (21):634-38.

Threlfall EJ, Rowe B, Ward LR. A comparison of multiple drug resistance in salmonellas from humans and food animals in England and Wales, 1981 and 1990. *Journal of Epidemiological Infections* 1993;111:189-97.

Threlfall EJ, Ward LR, Rowe B. Increasing incidence of resistance to trimethoprim and ciprofloxacin in epidemic Salmonella typhimurium DT104 in England and Wales. *Eurosurveillance* 1997;2:81-4.

Van den Bogaard AE, Mertens P, London NH, Stobberingh EE. High prevalence of colonization with vancomycin- and pristinamycin-resistant enterococci in healthy humans and pigs in The Netherlands: is the addition of antibiotics to animal feeds to blame? *Journal of Antimicrobial Chemotherapy* 1997;40(3):454-6

Vasallo FJ, Martin-Rabadan P, Alcala L, Garcia-Lechuz JM, Rodriguez-Creixems M, Bouza E. Failure of ciprofloxacin therapy for invasive nontyphoidal salmonellosis. *Clinical Infectious Diseases* 1998;26(2):535-6

Wall PG, Morgan D, Lamden K, et al. A case control study of infection with an epidemic strain of multiresistant Salmonella typhimurium DT104 in England and Wales. *Communicable Disease Report Review* 1994;4:R130-R135.

Wegener HC, Aarestrup FM, Jensen LB, Hammerum AM, Bager F. Use of antimicrobial growth promoters in food animals and Enterococcus faecium resistance to therapeutic antimicrobial drugs in Europe. *Emerging Infectious Diseases* 1999 (in press).

Annex 1

Welton LA, Thal LA, Perri MB, Donabedian S, McMahon J, Chow JW, Zervos MJ. Antimicrobial resistance in enterococci isolated from Turkey flocks fed virginiamycin.*Antimicrobial Agents Chemotherapy* 1998;42(3):705-8

WHO 1997a. Use of Quinolones in Food Animals and Potential Impact on Human Health: *Report of a WHO Meeting*, Geneva, Switzerland, 2-5 June 1998, WHO/EMC/ZDI/98.10.

WHO 1997b. Use of Quinolones in Food Animals and Potential Impact on Human Health: *Report and Proceedings of a WHO Meeting*, Geneva, Switzerland, 2-5 June 1998, WHO/EMC/ZDI/98.12.

WHO 1998a. The Medical Impact of the Use of Antimicrobials in Food Animals: *Report of a WHO Meeting*, Berlin, Germany, 13-17 October 1997, WHO/EMC/ZOO/97.4.

WHO 1998b. The Medical Impact of the Use of Antimicrobials in Food Animals: *Report and Proceedings of a WHO Meeting*, Berlin, Germany, 13-17 October 1997, WHO/EMC/ZOO/97.4.

WHO 1998c. Outbreak of quinolone-resistant, multiresistant Salmonella typhimurium DT104, Denmark. *Weekly Epidemiological Record* 1998;73:327-8.

7. Microbial

Baquero F, Negri MC, Morosini MI, Blazquez J. The antibiotic selective process: concentration-specific amplification of low-level resistant populations. In: Antibiotic resistance: origins, evolution, selection and spread. Wiley, Chichester (Ciba Foundation Symposium 207) 1997:93-111.

Chow JW, Fine MJ, Shlaes DM, Quinn JP, Hopper DC, Johnson MP, Ramphal R, Wagener MM, Miyashiro DK, Yu VL. *Enterobacter* bacteremia: clinical features and emergence of antimicrobial resistance during therapy. *Annals of Internal Medicine* 1991;115:585-590.

Loulergue J, Audurier A, DeLarbre JM, De Gialluly C. Changes in microbial ecology and use of cloxacillin. *Journal of Hospital Infection* 1994;27:275-283.

Olsen B, Weinstein RA, Nathan C, Kabins SA. Broad-spectrum beta-lactam resistance in *Enterobacter*: emergence during treatment and mechanisms of resistance. *Journal of Antimicrobial Chemotherapy* 1983;11:299-310.